

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 January 2006 (26.01.2006)

PCT

(10) International Publication Number
WO 2006/008749 A1

(51) International Patent Classification⁷: C07D 501/18

(21) International Application Number:

PCT/IN2004/000209

(22) International Filing Date: 16 July 2004 (16.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): HETERO DRUGS LIMITED [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500018, Andhra Pradesh (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PARTHASARADHI REDDY, Bandi [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500018, Andhra Pradesh (IN). RATHNAKAR REDDY, Kura [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500018 (IN). RAJI REDDY, Rapolu [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500018 (IN). MURALIDHARA REDDY, Dasari [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500018 (IN). MURALI, Nagabelli [IN/IN]; HETERO DRUGS LIMITED, Hetero House, 8-3-166/7/1, Erragadda, Hyderabad 500 018 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

PI, PL, PT, RO, RU, SC, SD, SE, SG, SK, SI, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PREPARING PURE CEPHALOSPORINS INTERMEDIATES

(57) Abstract: The present invention relates to a process for preparing key intermediates for cephalosporin antibiotics substantially free of undesired delta A² isomer. Thus, 7-aminocephalosporanic acid (7-ACA) is silylated with hexamethyl disilazane in cyclohexane at room temperature. (6R,7R)-3-[(Acetoxy)methyl]-7-(trimethylsilyl)aminoceph-3-em-4-oic acid obtained is reacted with the mixture of N-methylpyrrolidine and trimethylsilyliodide in cyclohexane, desilylated with isopropyl alcohol and treated with hydrochloric acid to obtain [6R-(6a,7b)]-l-[[7-Amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-l-methylpyrrolidinium inner salt hydrochloride. [6R-(6a,7b)]-l-[[7-Amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-l-methylpyrrolidinium inner salt hydrochloride is N-acylated with syn-2-(2-aminothiazol-4-yl)-2-methoxyimino acetic acid 2-benzothiazolyl thioester (MAEM) followed by treatment with hydrochloric acid to give cefepime dihydrochloride monohydrate.

A1

WO 2006/008749